DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

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By Certified Mail-Return Receipt Requested
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CBER-07-005

Warning Letter

Stephen M. Cardamone, D.O.
Chief Medical Officer and Senior Vice President
Wheaton Franciscan Healthcare
3421 West Ninth Street
Waterloo, Iowa 50702

Dear Dr. Cardamone:

This letter describes the results of a Food and Drug Administration (FDA) inspection of the [redacted] Institutional Review Board for [redacted] and Covenant Medical Center (hereafter referred to as "the IRB") that was conducted from September 13 to 15, 2006. FDA investigator Barbara Breithaupt conducted an inspection of the IRB to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 56. The inspection was part of FDA's Bioresearch Monitoring Program, which includes inspections designed to review IRB operations for clinical studies using investigational products and for the protection of human subjects.

The FDA investigator issued and discussed the Form FDA 483, Inspectional Observations, with you and other staff members of your institution at the end of the inspection. We have reviewed the inspection report, the Form FDA 483, and the letter dated October 12, 2006 from [redacted] Outpatient Treatment Services, written in response to the Form FDA 483.

We have determined that the IRB significantly violated applicable federal regulations governing the operation and responsibilities of IRBs as published under 21 CFR Part 56 (available at http://www.gpoaccess.gov/cfr/index.html). The applicable provisions of the CFR are cited for each violation. We are addressing this letter to you because, under 21 CFR 56.120(c), the parent institution is presumed to be responsible for the operation of the IRB.

1. **The IRB failed to follow adequate written procedures for conducting its initial and continuing review of research. [21 CFR § 56.108(a)].**

   A. The IRB did not follow the IRB's written procedures in its "Human Research Review Manual" dated 11/16/04. For example, these procedures required the following:

- the IRB must notify investigators in writing of its decision to approve or require modifications in a research study (pages 16 and 25);
- the meeting minutes must include action such as discussion of SAE reports (page 12);
- revisions to informed consent forms must include the revision dates noted on each page (page 20);
- the IRB must maintain copies of correspondence between the IRB and the investigators, records of continuing review activities, approved informed consent documents, progress reports, reports of injuries to subjects (page 26); and
- the IRB is required to terminate the research study protocol when an investigator fails to adhere to submit reports required by the IRB (page 22).

B. The IRB's written procedures require that the IRB receive and review continuing review reports submitted by clinical investigators and make approval determinations based on the material reviewed. According to the IRB's written procedures, continuing review reports must include, among other items, the current status of the study, a list of all enrolled subjects, brief summaries of the research study progress, and a summary of the "severe" Serious Adverse Drug Experiences. As part of its normal operations, the IRB did not follow or enforce these requirements. IRB staff reported that continuing review approvals were usually based on verbal comments during the IRB meetings, rather than the required continuing review reports. The IRB approved the continuation of studies with no record of the status of the studies, the adverse events experienced by the subjects, or the number of subjects screened and enrolled.

We note that your memorandum dated 9/15/06 to the IRB, submitted with the 10/12/06 response, states "...no items will come before the IRB for action unless all regulatory requirements for documentation have been submitted in advance for the agenda." We remind you that the IRB's written procedures require the IRB members to review the agenda materials to be discussed prior to each IRB meeting and to actively participate in IRB meetings. In your response to this letter, please include a copy of any modifications to the IRB's written procedures.

2. **The IRB failed to prepare and maintain adequate documentation of IRB activities. [21 CFR 312 § 56.115(a)].**

A. The IRB failed to maintain copies of some original and revised protocols, copies of some consent forms approved by the IRB, and some serious adverse event reports that occurred at your institution, as required in 56.115(a)(1). During the inspection many of these documents had to be obtained directly from the clinical investigators.

The 10/12/06 response states that the IRB will now require investigators to submit annual reports prior to the anniversary date of the protocol and that the IRB facilitator will track these reports. We remind you that the IRB's written procedures require the IRB to immediately terminate a research study protocol if the investigator fails to submit a continuing review report prior to the expiration date of the IRB's approval of the research study.

B. The meeting minutes are not in sufficient detail to adequately document the IRB's actions, as required in 56.115(a)(2). The IRB meeting minutes do not identify the title of the study, version of the study protocol or version of the consent forms that the IRB discussed and/or approved during the meetings. For example, the meeting minutes for 3/9/05, 6/1/05, and 9/28/05 do not specify the study title that the IRB renewed for another year. Without a means of clearly identifying which study is being discussed, the IRB may not be able to track the actions required by the IRB and assess the subjects' safety in the studies. Similarly, "annual renewals" are listed with no supporting information and with no indication whether the annual review and approval for a study was given after evaluation of study updates such as the therapy, eligibility, informed consent, and adverse events. Elsewhere in the minutes, adverse events are listed by product and often lack the protocol identifier. There is no documentation that the adverse events are linked to a specific protocol and are discussed by the IRB. The minutes are written in such a way that presume that IRB members can link the protocol number to the name of the test article.

C. The IRB failed to maintain adequate documentation of IRB activities on continuing review of research, required in 56.115(a)(3). Some IRB records lack critical information such as the title of the study that was reviewed and approved, the clinical investigator to whom the review and approval was addressed, interval between the continuing review and approval.

D. The IRB did not maintain adequate documentation of all correspondence between the IRB and the investigators required by 56.115(a)(4). Some available IRB approval letters do not indicate to whom the letter was issued because the approval letters include the names of several co-investigators.

3. **The IRB failed to review proposed research at convened meetings at which a majority of the members of the IRB were present, including at least one member whose primary concerns are in nonscientific areas. [21 CFR § 56.108(c)].**

The IRB approved research by votes on new protocols on at least five meeting dates, 5/12/04, 11/17/04, 1/12/05, 6/1/05, and 11/30/05, during meetings that did not include a member whose primary concerns are in nonscientific areas.

The IRB letter states that the nonscientific member will be required to be present for all meetings and that ongoing compliance will be monitored by the IRB facilitator. Your corrective actions appear to be adequate, if successfully implemented.

4. **The IRB failed to require that information given to subjects as part of informed consent is in accordance with the provisions of 21 CFR § 50.25 and is documented in accordance with 21 CFR § 50.27. [21 CFR § 56.109(b)-(c)].**

The IRB approved the conduct of research without determining that informed consent would comply with the requirements of 21 CFR § 50.25 and be documented in accordance with 21 CFR § 50.27. For example, the IRB approved protocol [redacted] but did not review the informed consent form that would be used by the study participants.

The 10/12/06 response acknowledges deficiencies in the informed consent document practices. The letter proposes corrective actions such as implementation of a protocol submission checklist. The IRB should incorporate the revision in its written procedures and ensure compliance with any such actions instituted.

We recommend that the IRB record the number of votes on each of the action taken by the IRB and avoid recording the votes as a block voting such as the record for all [redacted] annual renewals conducted on 3/29/05.

We also recommend that the IRB's written procedures be revised to include (1) a tracking number for each study that the IRB intends to review to facilitate review and recordkeeping requirements; (2) documentation of training records of IRB members; and (3) a date on the first page of procedures so the IRB staff will know they are using the most recent version.

This letter is not intended to contain an all-inclusive list of deficiencies in the operations of the IRB.

Please notify this office in writing, within fifteen (15) business days of receipt of this letter, of the actions you have taken or plan to take to bring the IRB into compliance with FDA requirements. Please provide the requested information, and include a copy of any revised documents, such as written procedures, revised roster, and recent meeting minutes with your response. Also, for any plans of action, please include the projected completion dates for actions to be accomplished.

Your failure to adequately respond to this letter may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions could include FDA withholding approval of new studies reviewed by your IRB that are subject to Parts 50 and 56 of the FDA regulations, prohibiting the admission of new subjects to ongoing studies that are subject to 21 CFR Parts 50 and 56, terminating all ongoing studies approved by your IRB, and initiating regulatory proceedings for disqualification of your IRB.

Please send your written response to:

Ms. Bhanu Kannan
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, Maryland, 20852-1448
Telephone: (301) 827-6221

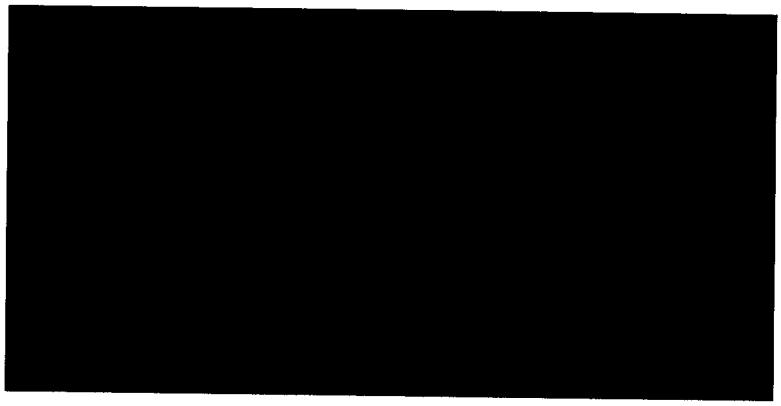
We request that you send a copy of your response to the FDA District Office listed below.

Sincerely,

for

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Cc: John Thorsky, District Director
Food and Drug Administration
11630 W. 80th Street
Lenexa, Kansas 66214



Kristina Borror, Ph.D., Director
Division of Compliance Oversight
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, MD 20852